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Three-Generation Family With Resemblance to Townes-Brocks Syndrome and Goldenhar/Oculoauriculovertebral Spectrum

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The Townes-Brocks syndrome (TBS) is comprised of a triad including characteristic anal, thumb, and ear anomalies. There are many other organ system abnormalities which may be present. However, the literature does not emphasize craniofacial findings except with reference to the typical ear configuration. A three-generation family is described in which craniofacial manifestations were prominent and a Goldenhar-like condition was considered as the most likely diagnosis. However, with the recent birth of an affected male who had an imperforate anus, the diagnosis of TBS was also considered. The family manifests a variety of Goldenhar-like findings, including epibulbar dermoids, hemifacial microsomia, preauricular tags, macrostomia, and micrognathia in addition to classical ear, radial, and anal findings of TBS. We report on this family to point out a possible biological relationship of these two conditions. © 1996 Wiley-Liss, Inc.

KEY WORDS: Townes-Brocks syndrome, Goldenhar syndrome, oculoauriculovertebral spectrum, epibulbar dermoids, hemifacial microsomia

INTRODUCTION

Townes-Brocks syndrome (TBS) is characterized by anomalies of the external ear, anus, and thumb [Townes and Brocks, 1972]. There is wide variation in the malformations of these three systems, and a number of other organs can be involved. However, in the literature [Townes and Brocks, 1972; Silver et al., 1972; Reid and Turner, 1976, 1977; Townes, 1977; Pinsky, 1977; Kurnit et al., 1978; Walpole and Hockey, 1982; Moeschler and Clarren, 1982; Monteiro de Pina-Neto, 1984; Fraser and Cooper, 1985; Aylsworth, 1985; Hersh et al., 1986; Friedman et al., 1987; Barakat et al., 1988; DeVries-Van der Weerd et al., 1988; Johnson and Sherman, 1989; Ferraz et al., 1989; Saal et al., 1990; Konig et al., 1990; O'Callaghan and Young, 1990, Blackston et al., 1991; Cameron et al., 1991; Il'ina and Laziuk, 1992; Kotzot et al., 1992; Lenz, 1993; Gabrielli et al., 1993; Serville et al., 1993], there is little emphasis on the craniofacial manifestations of this syndrome nor of its occasional resemblance to Goldenhar/oculoauriculovertebral spectrum (G/OAVS) [Cohen et al., 1989]. In this report, we describe a family with overlapping findings of TBS and G/OAVS.

CLINICAL REPORT

The propositus (IV-1, Fig. 1) was first encountered as a newborn male in the postoperative period following a minor surgical procedure to open an imperforate anus covered by a thin membrane. The baby was referred because of other minor anomalies. He was born to a 24-year-old woman following a 37-week pregnancy. Birth weight was 2,810 g, length 46.5 cm, and OFC 33.5 cm. A two-vessel umbilical cord was noted. The overall appearance was normal except for some specific anomalies (Fig. 2). There was very mild facial asymmetry with the left side being smaller (Fig. 2A). The ears were unusual and small with overfolding of the helix more prominent on the right. A small preauricular tag was present anterior to this ear (Fig. 2B). Close examination of the left eye revealed an epibulbar dermoid near the inferior outer canthus (Fig. 2C). Examination of the extremities showed triphalangeal thumbs deviated to the ulnar side (Fig. 2D). The toes were unusual in that the lengths were equal and the width of the fourth toe was increased (Fig. 2E). Examination of the anus showed redundant skin at the mucocutaneous junction. A small chordee of the penis was present (Fig. 2F). Internal anomalies included a small ventricular septal defect and significant hearing loss with lack of brainstem response to higher frequency tones under 60–65

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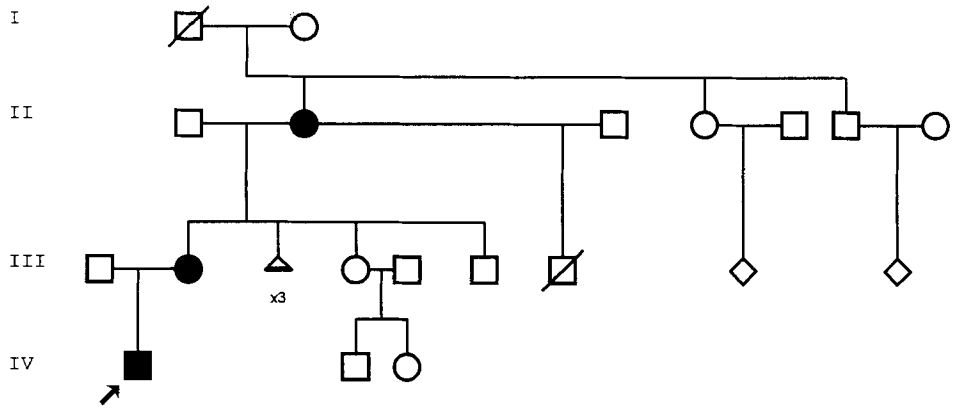

Fig. 1. Pedigree of family. Members affected with Townes-Brocks syndrome (black) are propositus (IV-1), his mother (III-2), and his maternal grandmother (II-2). Individual III-9 died of unknown causes shortly after birth but may have had spina bifida.

db. Renal ultrasound and routine chest and abdominal radiographs were normal.

Of considerable interest was the family history. The family had come to attention 14 years prior to the birth of this baby when his mother (III-2, Fig. 1) was referred for genetic evaluation. She was born about two weeks early with a birth weight of 1,800 g. A two-vessel cord was found. At age 11 years she presented with short stature (3rd centile height), minor anomalies, and developmental delay with minimal unaided sensorineural hearing loss. Specific craniofacial findings (Figs. 3 and 4) included overfolded pinnae and small ears, abnormal tragus (with history of preauricular and tragal tags on the right and postauricular tag on the left; Fig. 3A); facial asymmetry (smaller right side; Fig. 3B); epibulbar dermoids bilaterally (Fig. 3C); micrognathia, and macrostomia with lateral extension more prominent on the right (Fig. 3A). The thumbs were triphalangeal with a previously removed, rudimentary, supernumerary digit that had been attached to the right thumb (Fig. 3D), and there was a report of midline clefting of the uterus. The anus was normal. A WISC full-scale IQ of 84 was obtained at age 10. The mother was reexamined at age 24 years when she sought genetic counseling during her pregnancy. The additional finding of microcephaly (OFC 52 cm, 2nd centile) was noted at that time.

The maternal grandmother (II-2, Fig. 1) was equally interesting. She had a moderate, aided, sensorineural hearing loss. Craniofacial findings (Figs. 4 and 5) included overfolded pinnae, small ears, preauricular tags (Fig. 4A); a unilateral epibulbar dermoid (right, Fig. 4B); and micrognathia without significant facial asymmetry. The thumbs were triphalangeal (Fig. 4C) and the great toe on the left was bifid representing syndactyly of toes 1 and 2 or absence of 2 (Fig. 4D). Genitourological abnormalities included urethral stenosis and septate uterus. Examination of the anus revealed redundant skin. Other skeletal anomalies included extra ribs, scoliosis, and short stature (height 147 cm, less than 2nd centile). OFC was normal at 53.5 cm. A thyroidectomy had been performed because of hyperfunction, and there was a history of three miscarriages. There were two other normal children born to this woman. One baby died within days of birth for unknown reasons (possible spina bifida) after a 7-month pregnancy with a birth weight of 1,360 g (Fig. 1).

Unfortunately, given our consideration of a Mendelian disorder in this family, karyotypes were not obtained at the time of diagnostic consultation. We have been unsuccessful in recent attempts to contact the family.

DISCUSSION

Before the birth of the male grandson affected with imperforate anus, this family had been diagnosed to have a Goldenhar-like syndrome inherited in an autosomal dominant fashion. Given this additional anomaly in the grandson, the diagnosis of TBS was strongly considered because of dominant inheritance in three generations of triphalangeal thumbs and abnormal ears. However, there are many additional manifestations in this family which highlight an overlap of TBS and G/OAV Spectrum.

In G/OAVS, radial and anal anomalies are listed as low frequency findings, and congenital heart disease and genitourinary malformations are not uncommon [Cohen et al., 1989]. Therefore, one could argue that this family actually has this condition. However, striking facial asymmetry and vertebral defects are not present in this family making this diagnosis less tenable. It is interesting that epibulbar dermoids are present, which have been considered by some [Gorlin et al., 1963; Finegold and Baum, 1978] to be mandatory for a diagnosis of Goldenhar/OAV Spectrum and, while not pathognomonic of this condition, are fairly specific to G/OAVS and are seen in few other syndromes.

With regard to TBS, facial asymmetry and epibulbar dermoids have not been observed in this condition. However, all three affected relatives exhibit ear anomalies and triphalangeal thumbs, and two have abnormal anal findings, which is the third manifestation of the diagnostic triad in this syndrome. The additional

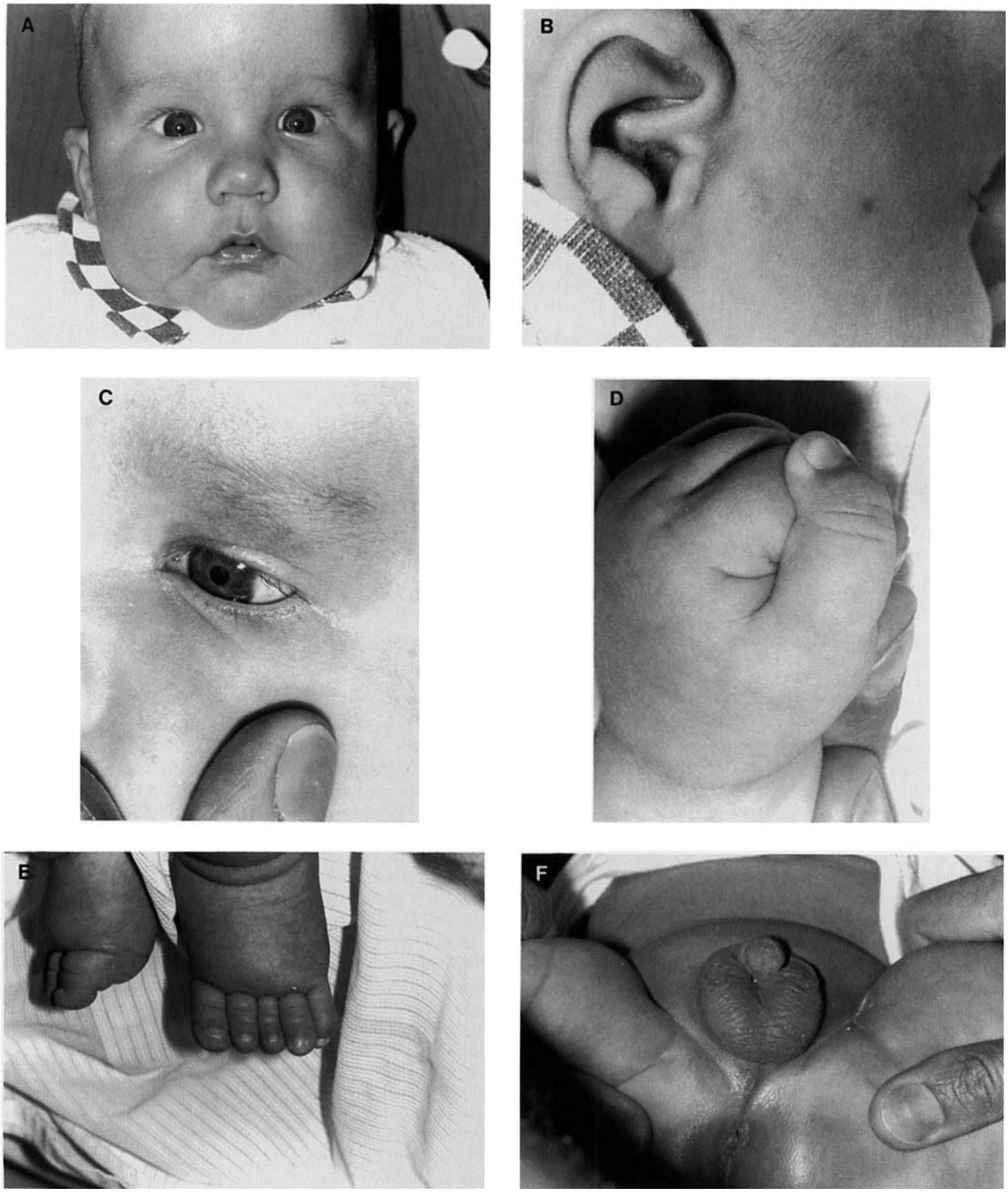

Fig. 2. Propositus (IV-1, Fig. 1), age 3 months. **A:** Note mild facial asymmetry, overfolded pinnae. **B:** Small ear, unusual tragus with small preauricular tag. **C:** Lateral scleral epibulbar dermoid encroaching upon limbus of cornea. **D:** Triphalangeal thumb, ulnar deviation. **E:** Unusual toes of equal size with increased width of #4. **F:** Penile chordee and redundant mucosal folds at anal opening.

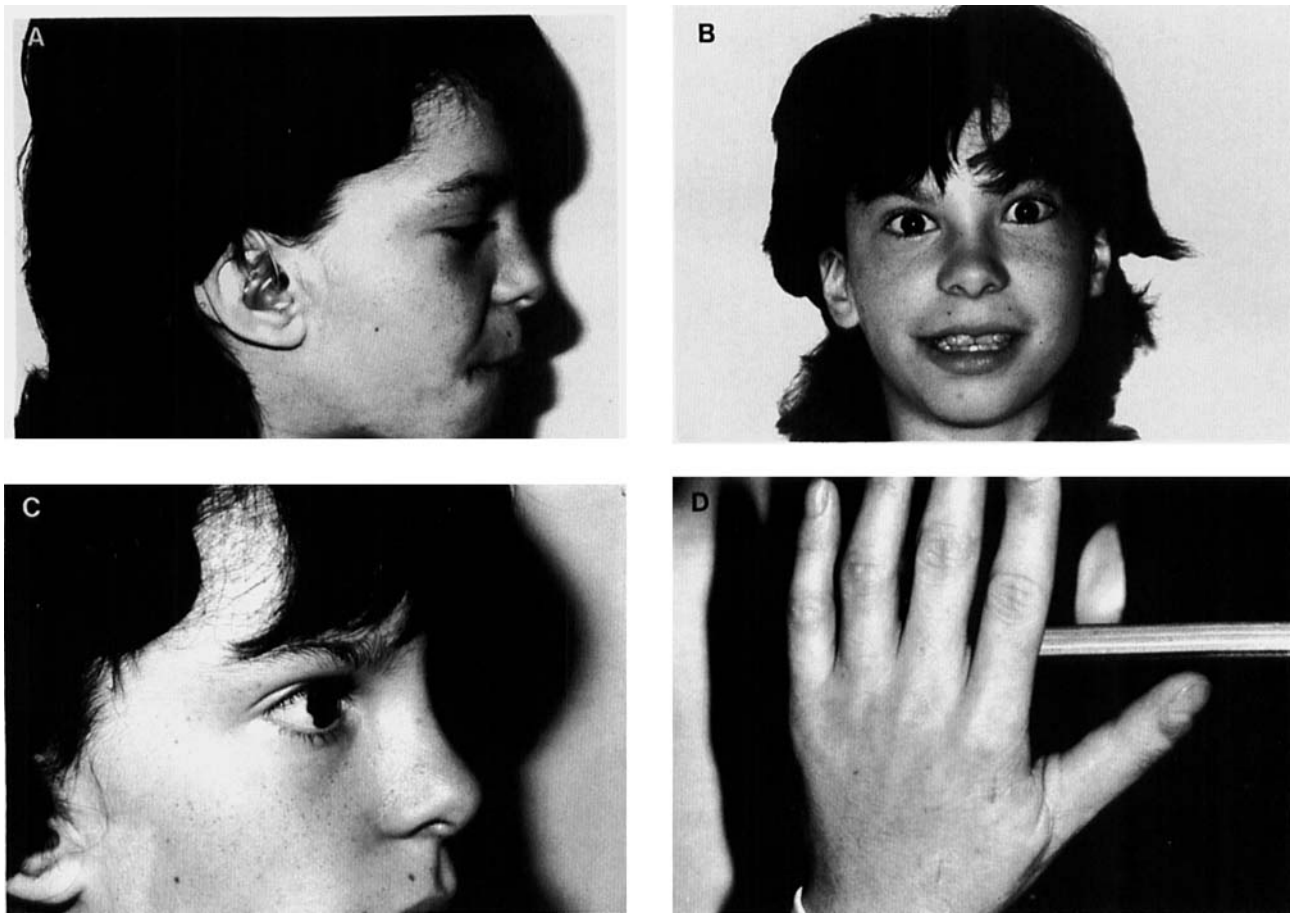

Fig. 3. Mother of propositus (III-2, Fig. 1) at age 11 years. **A:** Small ear with irregular tragus (previous operative repair of tragus and preauricular tags), macrostomia with lateral oral cleft. **B:** Facial asymmetry. **C:** Epibulbar dermoid. **D:** Triphalangeal thumb (postoperative view).

craniofacial anomalies in this family, including micrognathia, macrostomia, and deafness, have all been reported in TBS families. Likewise, short stature, mild mental deficit, congenital heart and genitourinary anomalies, and the interesting foot anomalies in the grandmother are all observed as occasional abnormalities. The extra ribs and scoliosis in the grandmother are apparently unique to this family and represent additional findings overlapping with G/OAVS.

There are other families reported in the literature which are not readily classified but illustrate this overlap in findings of TBS and G/OAVS. Moeschler and Clarren [1982] reported on a family with hemifacial microsomia combined with radial ray defects. Facial manifestations included abnormal ears, multiple preauricular tags and pits, skin tags along the mandibular angle, and unilateral micrognathia. Triphalangeal thumbs were present with unilateral thumb polydactyly, and the anus was slightly anteriorly placed. The mother had a similar constellation of anomalies with additional findings of hearing loss and abnormal toes, but normal anus. This family was described as having a discrete autosomal disorder with signs of G/OAVS combined with radial anomalies. There is strong resemblance of this family to the one described here, and therefore we believe a diagnosis of TBS could be considered for the family reported by Moeschler and Clarren. Fraser and Cooper [1985] described a family with facial asymmetry and unilateral microphthalmia with a proposita who also had an anteriorly displaced anus, irregular toes, and a digitalized (though biphalangeal) thumb. They considered this a case of TBS with microphthalmia, but overlap with G/OAVS is apparent with microphthalmia and facial asymmetry. More recently, Gabrielli et al. [1993] described a child born to normal parents who had facial asymmetry, abnormal ears, preauricular tags extending along the mandibular line, normal hands, and anteriorly displaced anus. Vertebral anomalies were not present, making G/OAVS difficult to diagnose, and there were no thumb anomalies to indicate a diagnosis of TBS. For this case the authors postulate partial expression of each of these syndromes due to an incomplete contiguous gene microdeletion.

In conclusion, we wish to draw attention to this family and the family described by Moeschler and Clarren [1982] who have overlapping findings of G/OAVS and TBS. We have considered the diagnosis of TBS in our

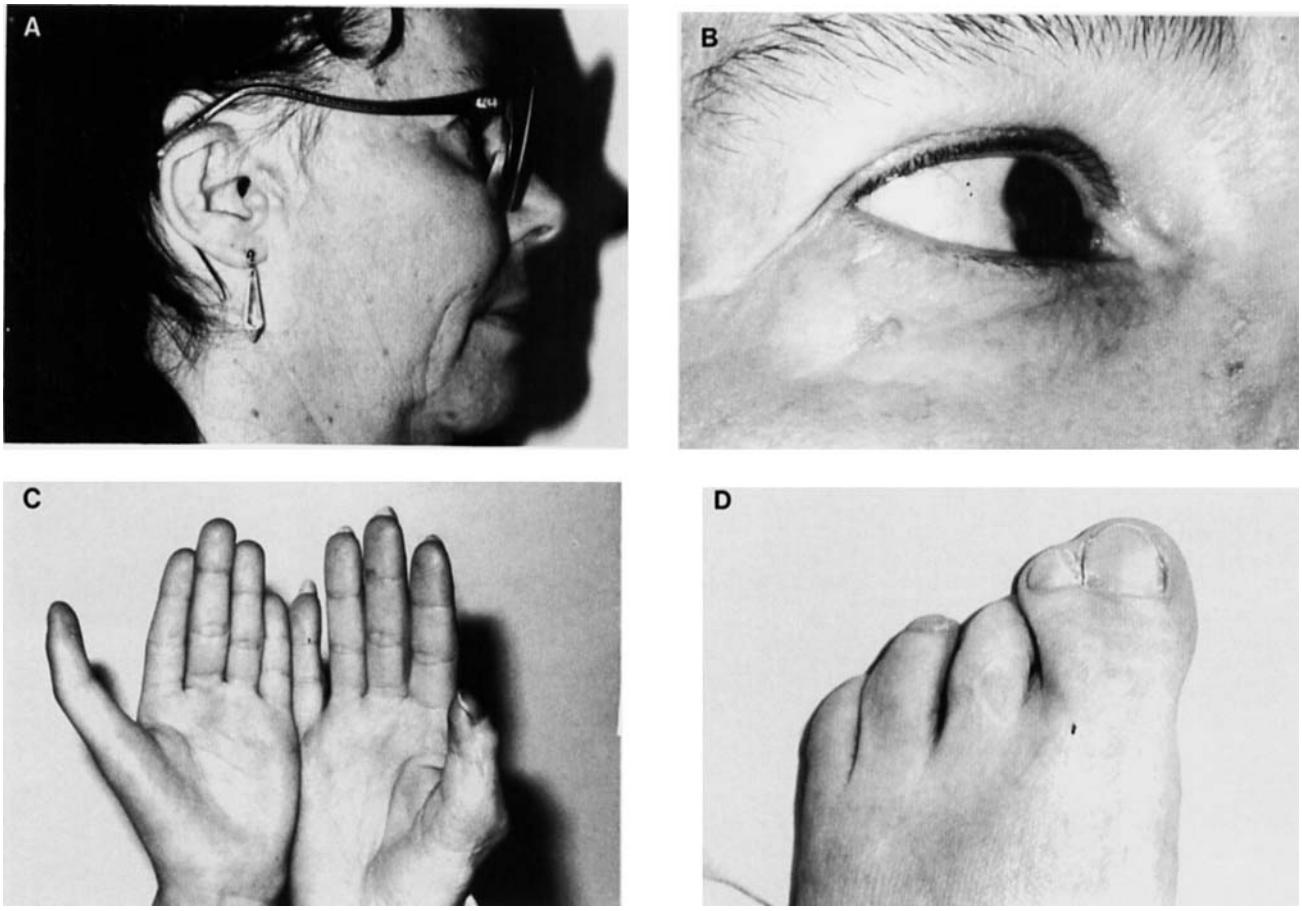

Fig. 4. Grandmother of propositus (II-2, Fig. 1) at age 50 years. **A:** Small ears with overfolded pinnae, abnormal tragus, preauricular tags. **B:** Epibulbar dermoid. **C:** Triphalangeal thumbs (previous operative repair of left). **D:** Bifid left great toe with three normal digits.

family based upon the presence of the classical diagnostic triad, but are impressed at the additional signs of G/OAVS as illustrated by the micrognathia, macrostomia, facial asymmetry, preauricular tags, hearing loss, and epibulbar dermoids present in this family.

Fig. 5. Mother (III-2, Fig. 1) of propositus at age 25 years (**left**) and her mother (II-2, Fig. 1) at age 50 years.

Many TBS patients in the literature have some of these findings, and there are isolated cases that are difficult to categorize. Eventually, molecular analysis may be helpful in establishing a correct diagnosis for some families. For now, what limited gene mapping data are available do not point toward a common location for G/OAVS and TBS. A family with G/OAVS signs shows linkage near the branchio-oto-renal and trichorhinophalangeal/Langer-Gideon syndrome loci on chromosome 8q [Graham et al., 1994], and there have been two reports of chromosome 16q anomalies in TBS patients [Friedman et al., 1987; Serville et al., 1993]. Linkage studies of families with apparent autosomal inheritance of either clear-cut TBS or G/OAVS or of an overlapping presentation will be helpful in establishing the relationship between these conditions. Given the similarities, a biological relationship between these conditions, perhaps related to contiguous genes, could be postulated.

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